REMARKS/ARGUMENTS

Status of the Claims

Claims 21-34, 45, and 46 are now pending in the application. Applicants respectfully note that the first Office Action for this application was issued May 12, 2000, and thus this application has been in prosecution for over five years. During that time frame, claims 21-34 have been identified as allowable subject matter on no less than four separate occasions. Despite Applicants' claim amendments to reflect that allowable subject matter, all pending claims are now finally rejected. Applicants respectfully request reconsideration of the pending claims in view of the following remarks. The Examiner's comments in the final Office Action are addressed below in the order set forth therein.

The Rejections of the Claims Under 35 U.S.C. §103(a) Should Be Withdrawn

Claims 21-34, 45, and 46 stand rejected under 35 U.S.C. §103(a) as being obvious in view of Clark *et al.* (U.S. Patent No. 5,597,802; hereinafter the '802 patent). This rejection is respectfully traversed.

Applicants have discovered that pharmaceutical formulations that are buffered with succinate at the concentration ranges recited in these claims result in reduced pain on injection relative to those formulated with other buffers at similar concentrations. For instance, using a nociceptor activation model designed to predict the pain of injection produced by formulations, Applicants have demonstrated that injection of a 10 mM succinate IGF-I formulation is no more painful than injection of normal saline. See Example 4 and Figure 7. Additional data from a study in New Zealand white rabbits indicates that injection of IGF-I buffered with 10 mM succinate results in lower local irritant effects as compared to other commonly used buffers, such as sodium acetate. See Example 5 and Figure 8.

Applicants have previously made of record, and the Examiner has acknowledged, that the succinate concentration ranges recited in the pending claims are not specifically taught by the '802 patent. Accordingly, there must be some suggestion in this cited reference or knowledge generally available to one of ordinary skill in the art to modify this cited reference to arrive at

Applicants' claimed invention, wherein IGF-I or variant thereof is formulated with succinate at the claimed concentration ranges and in the pH range of 4.0 to 7.0.

The '802 patent lists succinate as a member of a Markush grouping of GRAS buffers that can suitably be used to practice the '802 invention. However, the only disclosure of a buffer concentration within the '802 patent resides in the specification at column 12, lines 14-26, wherein a preferred composition is disclosed. This composition comprises IGF-I and GH, an osmolyte, an inorganic salt and/or sugar alcohol, at least one stabilizer, a surfactant, and "about 5 to 100 mM of a buffer at about pH 5-6." Applicants respectfully submit that the reference to succinate within the context of a list of GRAS buffers merely invites experimentation; yet an invitation to experiment is not sufficient grounds to reject an invention as obvious. It is well settled in the case law that in order to render a claimed invention obvious within the meaning of 103, the prior art must contain some suggestion of the desirability and the manner of making the proposed modification. See, e.g., *In re Antonie*, 559 F.2d 618, 195 USPQ 6; *In re Taborski*, 183 USPQ 50; and *In re Murch,* 175 USPQ 89. Moreover, the mere fact that the prior art could be modified would not have made the modification obvious unless the prior art suggested the desirability of the modification. *In re Laekowski*, 10 USPQ2d 1397, 1398 (Fed. Cir. 1989). The '802 patent does not guide the skilled artisan to the recited range of succinate buffer that Applicants have discovered provides reduced pain upon injection relative to other commonly used buffers.

The Examiner reasons that one of skill in the art would obviously have chosen succinate buffer to formulate IGF-I at pH 5.0-6.0, as the pK2 of succinate buffer is pH 5.64 while acetate, having a pKa of 4.76, would not be suitable to buffer IGF-I at pH 6.0 (Office Action mailed March 4, 2005, at page 5). Applicants respectfully disagree with this line of reasoning.

It is readily apparent that the teachings of the '802 patent *as a whole* do not provide the requisite motivation to lead one of skill in the art to formulate IGF-I or biologically active variant thereof in a succinate buffer at the claimed concentration ranges. Nor does this patent provide the requisite motivation to formulate IGF-I at pH 6.0 with a succinate buffer at a concentration of 5 to 100 mM as asserted in the Office Action. To the contrary, Applicants maintain that this cited patent teaches away from Applicants' claimed invention, as it clearly teaches the

advantages of formulating IGF-I with a sodium acetate buffer in the pH range of 5.0 to 5.5. The rationale for Applicants' position has been made of record, and is further supported in view of the following remarks.

Applicants once again point to the specification of the '802 patent in support of their contention that this patent teaches away from formulating IGF-I in a succinate buffer. As previously noted, a close reading of this patent demonstrates that the IGF-I compositions disclosed therein are preferably formulated with *an acetic acid salt buffer*, and *most preferably sodium acetate*. See the '802 patent at column 14, lines 12-30, and at column 14, lines 31-44, where the most preferred IGF-I formulation is taught. The '802 patent in fact teaches that the IGF-I formulation to be mixed with the GH solution preferably uses *50 mM sodium acetate* to ensure that the final pH in the IGF-I+GH mixture will not vary significantly from pH 5.4 to maintain solubility of both proteins (column 14, lines 38-42).

Further, the working examples in the '802 patent clearly teach away from Applicants' claimed invention, as they repeatedly describe the desirability of the increased potency and efficacy of IGF-I and/or IGF-I+GH compositions formulated with 50 mM sodium acetate buffer at a pH range of 5.0 to 5.5. It is noteworthy that not a single example sets forth the formulation of IGF-I with a succinate buffer at any concentration. Thus, Examples V through XIII investigate the *in vivo* potency of different formulations of recombinant human IGF-I, alone or in combination with GH, in anesthetized dwarf rats (Examples V-XI) or normal rats (Examples XII and XIII), where potency was evaluated in terms of the decrease in blood glucose level caused by an injection of any given IGF-I formulation.

Examples V and VI of this cited patent state that lower-dose IGF-I formulated at pH 5.0 in 20 mM sodium acetate buffer was more potent than the comparable dose of IGF-I formulated at pH 6.0 in 10 mM sodium citrate buffer (see column 24, lines 46-55, and column 25, lines 37-46, for formulations; see column 25, lines 14-25, and column 25, line 66, continuing through column 26, line 8, for comments regarding increased potency). Examples VII and VIII establish that the increased potency of the IGF-I formulated at pH 5.0 in 20 mM sodium acetate buffer when injected subcutaneously is likely due to the IGF-I being better absorbed from the subcutaneous injection site when formulated at the lower pH (see column 26, lines 60-64; and

column 27, lines 33-41). Example VIII concludes with the statement that "the absorption of IGF-I from the pH 6.0 formulation can unexpectedly be improved by a combination of pH and formulation changes" (column 27, lines 39-41), i.e., by lowering pH from 6.0 to 5.0 and changing the buffer from a sodium citrate buffer to a sodium acetate buffer.

The new formulation of IGF-I devised in Example IX of this cited patent reflects a change in the IGF-I formulation from pH 6.0, 10 mM sodium citrate buffer, to pH 5.4, 50 mM sodium acetate buffer. Again, this example concludes that "the pH 5.4 IGF-I formulation also was very well absorbed compared to the pH 6.0 formulation of IGF-I" (column 28, lines 29-30) and that "[c]hanging the pH of the formulation from pH 6 to pH 5.4 and changing the components of the formulation unexpectedly led to marked increases in biopotency" (column 28, lines 34-37). Example X confirmed the results of Example IX, and again concluded that "the pH 5.4 IGF-I formulation was very well absorbed compared to the pH 6.0 formulation of IGF-I" (column 29, lines 28-30) and that "[t]hese data confirm that the absorption of IGF-I from the pH 5.4 formulation is unexpectedly improved over that from the pH 6.0 formulation by a combination of pH and formulation changes" (column 29, lines 37-40).

Example XI further establishes the degree of increased potency of the pH 5.4, 50 mM sodium acetate buffer IGF-I formulation when administered by subcutaneous injection, concluding that "the efficacy of the IGF-I was improved about 3-fold using the pH 5.4 formulation of IGF-I" (column 30, lines 45-48). Example XII further establishes that the data obtained with the GH- and IGF-I-deficient dwarf animals could be extrapolated to a GH- and IGF-I-sufficient normal animal (column 31, lines 34-38). Example XIII further demonstrates that the improved potency of the IGF-I formulation having a pH of 5.4, and comprising 50 mM sodium acetate buffer can be maintained when the IGF-I is mixed and administered with GH (column 32, lines 19-29). Furthermore, the improved potency of this IGF-I formulation translated into an improved anabolic efficacy of injections of this IGF-I formulation. See Example XIV, at column 36, lines 53-58.

Thus, the inventors of the '802 patent stress that an acetic acid salt buffer is the preferred buffer for formulating IGF-I, and further teach the use of 50 mM sodium acetate to ensure that the final pH in the IGF-I+GH mixture will not vary significantly from pH 5.4 to maintain

solubility of these two proteins. Furthermore, all of the experimental data demonstrate the desirability of formulating IGF-I, with or without GH, at pH 5.0 or 5.4 with sodium acetate buffer in order to maximize the potency and efficacy of this protein when injected into an animal.

As to the Examiner's comment that one of skill in the art would necessarily be motivated to use succinate to buffer a formulation comprising IGF-I at pH 6.0, Applicants respectfully disagree. Where the inventors stress the desirability of formulating IGF-I at pH 5.0 to 5.5, and further demonstrate the suitability *and the pronounced biological advantage* of formulating this protein at that pH range using sodium acetate buffer, there is no motivation whatsoever to modify this reference to formulate IGF-I with a succinate buffer, particularly at pH 6.0, and particularly at the concentration ranges recited in Applicants' claimed invention.

In summary, Applicants respectfully submit that the '802 patent teaches a buffer concentration of 5 mM to 100 mM in the context of a preferred IGF-I+GH formulation, which the experimental data clearly demonstrates is a composition comprising sodium acetate buffer. While succinate is listed within a Markush grouping of suitable GRAS buffers, its suggestion is an invitation to experiment; there is no guidance to lead the skilled artisan to the succinate concentration range recited in Applicants' claimed invention that provides for reduced pain upon injection. The surprising finding that pain upon injection could be reduced by utilizing a particular buffer at a particular concentration was not obvious. Given the laundry list of buffers generically disclosed for use in practicing the invention of the '802 patent, and the broad concentration range of buffer disclosed in the context of a preferred IGF+GH formulation, one of ordinary skill in the art would not have a reasonable expectation of success in selecting the concentration ranges of the succinate buffer utilized by Applicants to reduce pain upon injection.

In view of these remarks, and further in view of all of the arguments previously made of record, Applicants respectfully submit that this rejection of the claims should be withdrawn.

CONCLUSION

In view of the aforementioned remarks, Applicants respectfully submit that the rejections of the claims under 35 U.S.C. §103 are overcome. Accordingly, it is submitted that this application is now in condition for allowance. Early notice to this effect is solicited. If in the opinion of the Examiner a telephone conference would expedite the prosecution of the subject application, the Examiner is invited to call the undersigned.

It is not believed that extensions of time are required, beyond those that may otherwise be provided for in documents accompanying this paper. However, in the event that additional extensions of time are necessary to allow consideration of this paper, such extensions are hereby petitioned under 37 C.F.R. §1.136(a), and any fee required therefore is hereby authorized to be charged to Deposit Account No. 16-0605.

Respectfully submitted,

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